with --Fig. 8A--, and "right" with --Fig. 8B--.

At Page 12, line 35, replace "FIG. 9 compares" with --FIGS 9A-9C compare--.

NE At page 13, lines 1-2, insert --(Fig. 9A)-- after "serum glucose", --(Fig. 9B)-- after "urea/nitrogen", and --(Fig. 9C)-- after "triglyceride".

IN THE CLAIMS

In claim 40, line 1, replace "11" with --10--.

In claim 61, line 2, replace "size" with --body weight--.

Please amend claim 10 as follows:

10 (amended). A purified or non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first ~~reference~~ vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first ~~reference~~ vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first ~~reference~~ vertebrate growth hormone

E

residue where

(i) a second ~~reference~~ vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first ~~reference~~ vertebrate growth hormone residue, and/or

Cont B1

(ii) the binding affinity for the first ~~reference~~ vertebrate growth hormone's receptor of a single substitution mutant of the first ~~reference~~ vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first ~~reference~~ vertebrate growth hormone,

B1 cont.

(c) a deletion of a residue which is not part of the alpha helixes of said ~~reference~~ vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and

(d) a deletion of a residue found in said first ~~reference~~ vertebrate growth hormone but deleted in a second ~~reference~~ vertebrate growth hormone,

said polypeptide having growth hormone receptor antagonist

activity,
with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

Please amend claim 29 as follows:

29 (amended). A purified or non-naturally occurring DNA molecule which comprise a coding sequence which encodes a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence which is at least 50% identical to the amino acid sequence of a reference vertebrate growth hormone, and wherein the amino acid position corresponding to amino acid Gly 119 of bovine growth hormone is [substituted with] an amino acid other than glycine or alanine, said polypeptide having growth hormone receptor antagonist activity,
with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

Please amend claim 35 as follows:

35 (amended). A purified or non-naturally occurring DNA molecule which comprises a coding sequence which encodes a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first ~~reference~~ vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and either

(II) any additional differences, if any, between said amino

acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first ~~reference~~ vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first ~~reference~~ vertebrate growth hormone residue where

(i) a second ~~reference~~ vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first ~~reference~~ vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first ~~reference~~ vertebrate growth hormone's receptor of a single substitution mutant of the first ~~reference~~ vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first ~~reference~~ vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said first ~~reference~~ vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and

(b) a deletion of a residue found in said first ~~reference~~ vertebrate growth hormone but deleted

in a second ~~reference~~ vertebrate growth hormone, said polypeptide having a statistically significant inhibitory effect on the growth of transgenic mice engineered to produce said polypeptide, as compared to the growth of equivalent nontransgenic mice,

with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, ~~Q122E, T123G~~, G126L, R127I and E129S.

Please amend claim 46 as follows:

46 (amended). A method of reducing [preventing a condition of a human or animal subject caused by excessive] growth hormone activity[, or treating a condition of a human or animal] in a mammalian subject [exacerbated by growth hormone activity,] which comprises administering to the subject a DNA molecule comprising a coding sequence encoding a mammalian growth hormone receptor antagonist which is a polypeptide, [according to claim 40], under conditions conducive to the integration of said DNA into the genome of one or more cells of said subject, said subject subsequently expressing a growth hormone activity-antagonizing and pharmaceutically acceptable amount of said polypeptide, said polypeptide having growth hormone antagonist activity in said subject,

where said polypeptide comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first reference vertebrate growth hormone, and

(B) differs therefrom solely in that

(I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said

amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

(i) a second reference vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first reference vertebrate growth hormone's receptor of a single substitution mutant of the first reference vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,

(c) a deletion of a residue which is not part of the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and

B4 Cont.

4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH family, and

(d) a deletion of a residue found in said first reference vertebrate growth hormone but deleted in a second reference vertebrate growth hormone

whereby the growth hormone activity in said subject is reduced.

B4 Cont

In claim 47, replace "condition is characterized by" with --mammal suffers from--, and delete ", and the antagonist has a growth-inhibitory effect".

In claims 48-50, and 53-56, replace "condition is" with --mammal suffers from--.

In claims 51 and 52, replace "antagonist inhibits the development of" with --mammal suffers from--.

Please amend claim 62 as follows:

62 (amended). A purified or non-naturally occurring DNA molecule comprising a coding sequence encoding a growth hormone receptor antagonist which is a polypeptide which comprises an amino acid sequence which

(A) is at least 50% identical with the sequence of a first reference vertebrate growth hormone, and

(B) differs therefrom solely in that

B5 (I) the amino acid position corresponding to amino acid Gly119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first vertebrate growth hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference vertebrate growth hormone residue where

(i) a second reference vertebrate growth hormone exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference vertebrate growth hormone residue, and/or

(ii) the binding affinity for the first reference vertebrate growth hormone's receptor of a single substitution mutant of the first reference vertebrate growth hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference vertebrate growth hormone,

B5 Cont.

(c) a deletion of a residue which is not part of the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the vertebrate GH

family, and

(d) a deletion of a residue found in said first reference vertebrate growth hormone but deleted in a second reference vertebrate growth hormone,

(e) an insertion of a residue at an insertion point outside the alpha helixes of said reference vertebrate growth hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such insertion point furthermore not being between conserved residues in the vertebrate GH family, and

B5 Cont.

(e) an insertion of a residue absent in said first reference vertebrate growth hormone but present in a second reference vertebrate growth hormone,

said polypeptide having growth hormone receptor antagonist activity,

with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S.

Please add the following new claims:

Sub E4 --63. The method of claim 46 in which the subject is human.

64. A purified or non-naturally occurring DNA molecule comprising a coding sequence encoding a polypeptide which comprises an amino acid sequence which

B6 (A) is at least 50% identical with the amino acid sequence of a first reference vertebrate hormone selected from the group consisting of vertebrate

growth hormones, prolactins, and placental lactogens, and

(B) differs therefrom solely in that

(I) the amino acid at the position corresponding to Gly 119 of bovine growth hormone is an amino acid other than glycine or alanine, and

(II) any additional differences, if any, between said amino acid sequence and the amino acid sequence of said first reference hormone, are independently selected from the group consisting of

(a) a substitution of a conservative replacement amino acid for the corresponding first reference hormone residue,

(b) a substitution of a non-conservative replacement amino acid for the corresponding first reference hormone residue where

(i) a second reference hormone defined by said group exists for which the corresponding amino acid is a non-conservative substitution for the corresponding first reference hormone residue, and/or

(ii) the binding affinity for the first reference hormone's receptor of a single substitution mutant of the first reference hormone, wherein said corresponding residue, which is not alanine, is replaced by alanine, is at least 10% of the binding affinity of the wild-type first reference hormone for that receptor,

B6 Cont

(c) a deletion of a residue which is not part of the alpha helixes of said reference hormone corresponding to helices 1(7-34), 2(75-87), 3(106-127) and 4(152-183) of porcine growth hormone, such deleted residue furthermore not being a conserved residue in the hormone family defined by said group, and

(d) a deletion of a residue found in said first reference hormone but deleted in a second reference hormone selected independently from said group of hormones,

B6 Cont

with the proviso that said polypeptide does not correspond to human growth hormone with all of the following substitutions and no others: Y111V, L113I, K115E, D116Q, E118K, E119R, G120L, Q122E, T123G, G126L, R127I and E129S,

said polypeptide having a vertebrate growth hormone antagonist activity--

REMARKS

1. The new proviso introduced by amendment into claims 10, 29, and 35, and presented ab initio in new claims 62 and 64, is intended to avoid any possibility of inadvertent anticipation by the hGH mutant "hPRL (111-129)" disclosed by Cunningham, et al., Science, 243:1330-6 (10 March 1989) (of record, see reference BI in 1449 attached to paper 7). Inspired by a questionable alignment of hGH with prolactin,[1] Cunningham, et al. mutated hGH at 12 positions in the region 111-129. One of these mutations was G120L.

Cunningham, et al. determined that this "hPRL (111-129)"

[1] cp. Cunningham Fig. 1 with Watahiki Fig. 3.